REMARKS

Claims 1, 3, 5 and 9 have been amended. Claims 4 and 16-66 have been canceled without prejudice. Subsequent to the entry of the present amendment, claims 1-3 and 5-15 will be pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

I. Amendment to the Claims

Claims 1, 3, 5 and 9 have been amended, per the suggestion of the Office, and to improve its form.

Claim 3 has been amended to recite the elected invention; and claim 4 has been canceled for being drawn to a non-elected invention.

No new matter has been added.

II. Rejections under 35 U.S.C. §112, First Paragraph (written description)

Claims 1-15 are rejected under on 35 U.S.C. §112, first paragraph as allegedly not containing a written description of the invention and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to practice the method in its best mode. The rejection is moot with regard to claim 4, which has been canceled. Applicants respectfully traverse the rejection as it applies to the pending claims.

It is submitted, that the present application provides a sufficient written description of the invention and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to practice the method in its best mode, for the following reasons.

MPEP §2163.02 states that:

> Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with *reasonable clarity* to those skilled in the art that, as of the filing

> date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

According to the Office Action, "the claims are directed to a method of modulating *any* myostatin activation, comprising contacting a *any* latent myostatin complex comprising *any* myostatin pro-peptide and *any* myostatin C-terminal fragment, and *any* metalloprotease that can cleave the myostatin pro peptide, with an agent that increases or decreases proteolytic cleavage of the pro-peptide by the metalloprotease, thereby modulating myostatin activation. ...The specification teaches the structure of only *several representative species* of such agents, which modulate metalloprotease. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the identifying characteristics of the agent (peptide), which inhibits cleavage of latent myostatin (page 4 of the Office Action)".

However, under MPEP §2163.04 (emphasis added):

> ... inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of <u>*fact*</u>. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is *presumed to be adequate*, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a *reasonable basis* to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

Applicants submit for the following reasons, that based on the "facts" described in the specification and known in the art at and prior to the time of the filing of the present invention, the skilled artisan would recognize from Applicants' disclosure a description which conveys *reasonable clarity* and shows that Applicants were in possession of the claimed invention.

First, with regard to the alleged function of "*any* myostatin activation", it is submitted that the function of myostatin is "common knowledge" or was well known in the art at the time of the filing of the present application. Applicants were the <u>first</u> to describe myostatin or GDF-8 function as a "negative regulator of skeletal muscle mass (page 12457, lines 6-7 of the first

paragraph of Exhibit A)". See Exhibit A, McPherron & Lee (1997) Double muscling in cattle due to mutations in the myostatin gene *PNAS* 94:12457-61. In fact, many of the seminal publications describing GDF-8/myostatin originated and are attributed to the Applicants. Exhibit A shows that myostatin is "highly conserved" across many species, suggesting conservation of myostatin function (page 12548, line first sentence of the first paragraph; and FIG.1). Exhibit A also describes that the "conserved C-terminal region" is the region following the RXXR proteolytic processing site (amino acids 263-266; page 12458, col. 1). The "C-terminal fragment", or its equivalent, the "C-terminal region", results in a polypeptide fragment that is about 109 amino acids in length. Later and more recent publications, e.g., Exhibit B, concur that the mature active form of myostatin, the "C-terminal fragment", consists of "109 amino acids... formed upon removal of the N-terminal prodomain by proteolytic cleavage at the tetrabasic ...site (sentence bridging pages 1-2 of Exhibit B)". See Exhibit B, Jin et al. (2004) Refolding and purification of unprocessed porcine myostatin expresses in *Escherichia coli* 35:1-10. It is noteworthy, that Jin et al. (Exhibit B), similar to other publications relating to GDF-8/myostatin, attributes the initial discovery of GDF-8/myostatin structure and function to the Applicants of the present invention. Thus, it was "common knowledge" and well known in the art at the time of the filing of the present application that the claimed "myostatin activation" refers to myostatin function as a negative regulation of skeletal muscle mass/growth.

With regard to "a latent myostatin complex" allegedly encompassing "*any* latent myostatin complex comprising *any* myostatin pro-peptide and *any* myostatin C-terminal fragment", it is submitted that these terms/phrases are also common or well known in the art at the time of the filing of the present application. Under MPEP §2111.01, "words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (discussed below); *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004). The plain meaning of "latent" is "something[which] is dormant and may become active in the future (http://encyclopedia.thefreedictionary.com/latent; Exhibit C)". Hence, the present application describing a "latent inactive myostatin complex, which comprises a myostatin pro peptide associated with a C-terminal myostatin polypeptide (paragraph [0013])" is *not*

inconsistent with the plain meaning of the term. Thus, "latent myostatin complex" is an inactive complex which "may become active in the future"; in this case, upon cleavage of the pro-peptide from the C-terminal fragment of the complex.

With regard to "a myostatin C-terminal fragment" allegedly encompassing "*any* myostatin C-terminal fragment", Applicants own publication (Exhibit A) describes that the "C-terminal region" or its equivalent, the "C-terminal fragment" is the region followed by the RXXR proteolytic processing site (amino acids 263-266), resulting in a polypeptide fragment that is about 109 amino acids in length. See page 12458, col. 1 of Exhibit A. Thus, as discussed above, the skilled artisan would clearly understand "a myostatin C-terminal fragment" to be the C-terminal fragment generated upon the proleolytic cleavage of full-length myostatin at the RXXR processing site.

With regard to "a metalloprotease" allegedly encompassing "*any* metalloprotease", again Applicants submit that the skilled artisan would not interpret "a metalloprotease" to be "any" protease. Example 1 clearly describes that the BMP-1/TLD metalloproteases (e.g., BMP-1, mTLD, mTLL-1 and mTLL-2) can cleave the pro-peptide in purified form or in a complex with the myostatin C-terminal dimer (i.e. a "latent myostatin complex"). Further, Example 4 describes that the conserved "RD" sequence is required for cleavage by the BMP-1/TLD metalloproteases. Thus, "any" metalloprotease would have to specifically cleave the pro-peptide.

Therefore, based on the foregoing, Applicants submit, that based on the "facts", the terms/phrases recited in the claims are consistent with the "plain meaning" and/or are described/defined in the specification such that "a person skilled in the art *would*.. recognize ... applicant's disclosure a description of the invention defined by the claims". MPEP §2163.04.

Accordingly, withdrawal of rejection of claims 1-15 under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §112, First Paragraph (written description)

Claims 1-15 are rejected under on 35 U.S.C. §112, first paragraph as allegedly lacking enablement. The rejection is moot with regard to claim 4, which has been canceled. Applicants respectfully traverse the rejection as it applies to the pending claims.

According to the Office Action (page 6):

> ... because the specification, while being *enabling for* a method of modulating activation of myostatin protein of SEQ ID NO:2, by a metalloprotease of human BMP-1 that can cleave the myostatin pro peptide, with peptide agents such as SEQ ID NO: 9-23 that decreases proteolytic cleavage of the pro-peptide by the metalloprotease BMP-1, thereby decrease myostatin activation, does *not reasonably provide enablement for* a method of modulating any myostatin activation, comprising contacting *any* latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, and *any* metalloprotease that can cleave the myostatin pro-peptide, with *any* agent that increases or decreases proteolytic cleavage of the pro-peptide by the metalloprotease, thereby modulating myostatin activation. ...

Under MPEP §2164.01, the test standard for determining whether the specification meets the enablement requirement ...: is the experimentation needed to practice the invention *undue* or *unreasonable*? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

It is submitted that the present application clearly describes how to make and use the claimed invention and is not *undue* or *unreasonable*. Example 1 describes that the BMP-1/TLD metalloproteases (e.g., BMP-1, mTLD, mTLL-1 and mTLL-2) can cleave the pro-peptide in purified form or in a complex with the myostatin C-terminal dimer (i.e. a "latent myostatin complex"). Example 2 describes that using a luciferase activity assay, "a comparison of the amount of myostatin activity present in the mTLL-1-treated sample and the degree of proteolytic processing of the pro peptide by mTLL-1 in this sample revealed that at least about 50% of the proteolytically-cleaved myostatin complex was active in the reporter assay (paragraph [0093] of the specification)". Example 3 describes a series of peptides based on myostatin pro-peptide sequence and retaining the "RD" BMP-1/TLD cleavage site: wild-type peptides (SEQ ID NO:9,

12, 15, 18 and 21); mutant peptides whereby Arginine residue has been mutated to a Glutamine residue (SEQ ID NO:10, 13, 16, 19 and 22); and mutant peptides whereby Aspartic residue has been mutated to an Alanine residue (SEQ ID NOs:11, 14, 17, 20 and 23). Example 4 is substantially similar to that published by Applicants in Wolfman et al. (December 23, 2003) Activation of latent myostatin by the BMP-1/tolloid family of metalloproteases *PNAS* 100(26):15842-46; Exhibit D). Example 4 and Exhibit D describe in detail the pro-peptide (pro-domain) cleavage site ("RD"; paragraph [0121] of the specification). Example 4 demonstrates that at least BMP-1, mTLL-1 and mTLL-2 were effective in cleaving the pro-peptide (paragraph [0123] - [0124] of the specification). Example 4 and Exhibit D also demonstrate that the latent myostatin complex is resistant to cleavage of the pro-peptide when the pro-peptide mutants having the Aspartate to Alanine mutant are used (paragraph [0125] of the specification). Further, *in vivo* studies demonstrate that the same mutant pro-peptide/Fc fusion protein effectively resulted in an animal with increased muscle mass, which is indicative of activation of the latent myostatin complex (paragraph [0127] – [0128] of the specification). Thus, because Applicants have described in detail the claimed invention, the skilled artisan can make and use "*any* myostatin pro-peptide" provided the pro-peptide contains the "RD" BMP-1/TLD cleavage site; "*any* myostatin C-terminal fragment" containing the RXXR processing site; "*any* metalloprotease" so long as it recognizes the "RD" cleavage site in the myostatin pro-peptide; and "*any* agent that increases or decreases proteolytic cleavage of the pro-peptide" can be explored. Therefore, the skilled artisan needs only to look to Applicants disclosure to make and use the claimed invention.

Accordingly, withdrawal of rejection of claims 1-15 under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §102

Claims 1-15 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Lee et al. (U.S. PGPUB 2002/0157126A1, publication 10/24/2002, filing date 4/24/01, claiming priority to 60/054,461 of 8/1/1997; hereinafter, "Lee"). The rejection is moot with regard to claim 4, which has been canceled. Applicants respectfully traverse the rejection as it applies to the pending claims.

To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, the claimed invention must be distinct from what is apparently inherent in the reference, and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980); and *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986).

According to the Office Action (page 9):

> Lee et al. disclose a method of modulating a myostatin activation, comprising contacting a latent myostatin complex comprising a myostatin pro-peptide and any myostatin C-terminal fragment, and a metalloprotease that can cleave the myostatin pro-peptide, with an agent (peptides) that increases or decreases proteolytic cleavage of the pro-peptide by the metalloprotease, thereby modulating myostatin activation.
> Lee et al. also teach that said metalloprotease is BMP-1.
> Lee et al. further teach a method of increasing myostatin activation.
> Lee et al. furthermore teach the method, which comprise *in vitro* and *in vivo* methods of myostatin activation.
> Lee et al. also teach administering the agent to a subject wherein the agent decrease proteolytic cleavage of the propeptide by the metalloprotease, thereby increase muscle mass and decrease fat content in said subject, wherein the subject an animal raised as a food source, such as avian or piscine species or ovine, porcine or bovine species or chicken or turkey or a human subject.

It is submitted that Lee cannot anticipate the claimed invention because Lee, for the following reasons, does not disclose *each and every element* of the claimed invention. The claimed invention is directed to, "[a] method of modulating myostatin activation, comprising contacting a latent myostatin complex comprising a myostatin pro-peptide and a myostatin C-terminal fragment, and *a metalloprotease* that can cleave the myostatin pro-peptide, with an agent that increases or decreases proteolytic cleavage of the pro-peptide by the metalloprotease, thereby modulating myostatin activation (emphasis added; claim 1)".

First, Lee must be *enabling* thus placing the allegedly disclosed matter in possession of the public. *Akzo N.V. v. U.S. Int'l Trade Comm'n* 1 USPQ2d 1241, 1245 (Fed. Cir. 1986). With the aid of the reference, one of ordinary skill in the art must be able to make the claimed invention without further experimentation. *In re Hall*, 781 F.2d 897, 899, 229 USPQ 453. Lee, however, does not describe *any* metalloproteases, let alone a metalloprotease capable of cleaving a myostatin pro-peptide as claimed. In fact, Lee also admits that "[r]elease of the C-terminal dimer from these inhibitory proteins [occurs] by *unknown mechanisms* ... (paragraph [0364] of Lee)". Thus, absent *any* description of a metalloprotease, the skilled artisan would not be put "in possession" of the alleged disclosed matter and cannot make the claimed invention "without further experimentation". *Akzo N.V.* and *In re Hall*. Therefore, Lee cannot anticipate the claimed invention because Lee is *not* enabling for what it purports to disclose.

Lee also cannot anticipate the claimed invention because Lee does *not* disclose *each and every element,* e.g., Lee does *not* disclose "a metalloprotease [that] can cleave the myostatin pro-peptide" as claimed. Lee *only* suggests that, "the myostatin C-terminal dimer and pro peptide *co-purified* rais[ing] the possibility that myostatin *may* normally exist in a similar latent complex [to TGF-β and its pro-peptide] and that the myostatin pro peptide *may* have inhibitory activity (emphasis added; paragraph [0160] of Lee, or Publication 2002/0157126)". In short, Lee *only* suggests (i.e. "may") that a latent myostatin complex exists based on a latent complex existing for TGF-β and its pro-peptide. Therefore, because Lee does not disclose *each and every element*, Lee cannot anticipate the claimed invention.

Lastly, the claimed invention is also not obvious in view of Lee since Lee does not establish a *prima facie* case of obviousness. For example, Lee provides *no* suggestion or motivation, either in the reference, as discussed above, or in the knowledge generally available to one of ordinary skill in the art (i.e. no known metalloprotease which cleaves the myostatin pro-peptide), to modify the reference or to combine reference teachings. There is *no* a reasonable expectation of success because Lee is *silent* with regards to *any* description of a metalloprotease. Lee also does *not* teach or suggest *all* the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. Hence, Lee cannot render the claimed invention obvious.

Accordingly, withdrawal of rejection of claims 1-15 under 35 U.S.C. §102 is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

A check in the amount of $180.00 is enclosed to cover the fee of an Information Disclosure Statement. No additional fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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